

Design of new pH-sensitive and cross-linked biomaterials for future medical applications

Over the last decade, polymer micelles attracted an increasing interest in drug pharmaceutical research because they could be used as efficient drug delivery systems^{1,2}. Micelles of amphiphilic block copolymers are supramolecular core-shell type assemblies of tens of nanometers in diameter³.

In principle, the micelles core is usually constructed with biodegradable hydrophobic polymers such as aliphatic polyesters, e.g. poly(ϵ -caprolactone) (PCL), which serves as a reservoir for the incorporation of various lipophilic drugs. Water soluble poly(ethylene oxide) (PEO) is most frequently used to build the micelle corona because it is very efficient in preventing protein adsorption at surfaces and in stabilizing the micelles in the blood compartment, giving rise to particles invisible to the body defence system (so-called stealthy or long circulating particles). Improvements of such simple systems however, rely on the development of novel chemistries and materials by advanced macromolecular engineering techniques⁴.

The tumour targeting of a cytotoxic agent refers to the passive accumulation of polymer nanocarriers to solid tumours (EPR effect) followed by active internalization in tumor cells. The internalization of the drug is required for cell death because most cytotoxic drugs act intracellularly. Accordingly, polymer micelles are usually modified by specific ligands. However, these ligands can decrease the micelles stealthiness and stability. No-specific ligands can be used if their exposition is modulated by the pH decrease typical of tumour tissues.

Lipophilic drugs are generally incorporated in the hydrophobic core of the micelles. The release of the drug is ruled by diffusion and degradation of the biodegradable polymer used as reservoir. Even if micelles get a high stability in aqueous media thanks to their low critical micellar concentration, the dissociation of micelles is not always preserved when they are injected in the blood compartment. The cross-linking of the core of micelles by disulfide bridges will provide the stability of micelles after the administration and will release the drugs intracellularly by enzymatic breaking of disulfide bridges.

This work consists in the development of new macromolecular architectures for the targeting of tumour cells. pH sensitive copolymers able to micellize so as non-specific ligand like biotin is exposed on their surface in response to pH decrease typical for tumour tissues (scheme) will be synthesized by the incorporation of pH-sensitive linkers like hydrazone or imine benzoic linkers. In addition, the core of these new micelles will be cross-linked by disulfide bridges to prevent dissociation around healthy cells and trigger the drug release inside tumour cells.

- [1] Kataoka, K.; Harada, A.; Nagasaki, Y. *Adv. Drug Delivery Rev.* **2001**, 47, 113-131.
- [2] Kwon, G. S.; Okano, T. *Adv. Drug Delivery Rev.* **1996**, 21, 107-116.
- [3] K. Van Butsele, R. Jérôme, C. Jérôme, *Polymer*, **2007**, 48(26), 7431-7443
- [4] C. Jérôme, P. Lecomte, *Adv. Drug Delivery Rev.*, **2008**, 60 (9), 1056-1076

S. C. is grateful to the "Fonds pour la Formation à la Recherche dans l'Industrie et dans l'Agriculture" (FRIA) for a fellowship.